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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (71)(72) Applicant and Inventor: KHAMAR, Bakulesh, Mafatlal [IN/IN]; 201 "Ashadha", Vasundhara Colony, Gulbai Tekra, Ellisbridge, Ahmedabad 380 006 (IN). | Published <i>With international search report.</i> |

(54) Title: THE PROCESS FOR MANUFACTURING FORMULATION OF TOPICAL BETA BLOCKERS WITH IMPROVED EFFICACY

(57) Abstract

Beta blockers are used as topical ophthalmic preparation for reducing Intra Ocular Pressure. B-blocker used for this purpose include timolol, levobunolol, carteolol, metipranolol. They reduce the aqueous production and thereby reduce I.O.P. They are commonly used as drops. Efficacy of topical B-blockers is dependent on concentration of drug in formulation. However, increasing the concentration of drug beyond approved dosage forms does not increase the efficacy significantly e.g. Timolol 0.5% has identical pressure lowering capacity as 1% Timolol. The attempts to improve pressure reduction efficiency of B-blockers has not met with success so far. The sustained release formulation of Timolol (Timolol XE) has resulted in amount of drug to achieve same therapeutic effect. However, none of the formulation has improved efficacy of drug for reducing I.O.P. The present invention relates to the process of manufacturing such formulation of B-blocker which improves its I.O.P lowering effect. The formulation so prepared is non-irritating and well tolerated. The process of manufacturing new formulation with improved efficacy involves use of carboprolol and preservative. The timolol 0.5% gel formulated using process was evaluated in normal as well as glaucomatous eyes. The reduction in I.O.P. is found to be approx. 15% more than found with drops in normal individuals. Similar findings are also observed in glaucomatous eyes.

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THE PROCESS FOR MANUFACTURING FORMULATION OF TOPICAL BETA BLOCKERS WITH IMPROVED EFFICACY.

The present invention relates to a process of manufacturing a formulation of Beta-blockers with improved efficacy and tolerance. Beta-blockers are used as topical ophthalmic preparations for reducing intraocular pressure.

The present invention is directed to manufacturing of a formulation containing Beta-blockers in such a way so that pressure lowering effects of Beta-blockers are improved. Beta-blockers are required to be used for a long time for reduction in I.O.P. Their prolonged use is associated with instability of tear film leading to dry eye. The present invention is also directed to manufacturing of a formulation containing Beta-blockers in such a way so that tear film is stabilized.

Beta-blockers are known to reduce I.O.P. mainly by reduction in aqueous secretion. This reduction in aqueous secretion is dose dependent. However, increasing the dosage beyond a point does not improve its capacity to reduce I.O.P. For timolol, levobunolol and Betaxalol it is achieved at 0.5% concentration for carteolol it is 1% and for metipranalol it is 0.3%. Increasing concentration beyond this does not result in further reduction in I.O.P.

The attempts made to improve its efficacy are not successful. In clinical situation when further reduction in I.O.P. is desired another drug like, Pilocarpine, Dipivefrin hydrochloride, Dorzdamide, Brimonidine, Latanoprost, etc. is added to it.

The formulations of Beta-blockers used are usually aqueous in nature.

There are sustained release preparations available for Beta-blockers. The formulation of pilocarpine in sustained release preparation is required to be doubled i.e. for I.O.P. reduction as much as 2% pilocarpine solution, 4% pilocarpine gel is required. Betaxolol is available as Betoptic-s and of timolol is Timoptic-XE. In both formulations vehicle used are different. With this it is possible to reduce concentration of Betaxolol used, but it is not possible to improve effect on I.O.P. Similarly, it is possible to reduce frequency of administration from twice a day to once a day with timoptic-XE. However, pressure lowering effect remains same. The formulations made with hydroxyl propyl methyl cellulose are found to be of no advantage compared to aqueous formulation.

Similarly, sustained release preparation of pilocarpine (Pilopine-HS gel) is also available. It contains Carbopol as a vehicle. The duration of action is prolonged but pressure reducing effect is reduced. To get the pressure lowering effect as much as aqueous solution, concentration of pilocarpine in sustained release preparation is required to be doubled i.e. for I.O.P. reduction as much as 2% pilocarpine solution, 4% pilocarpine gel is required.

The objective of present invention is to provide formulation of Beta-blockers with improved efficacy.

The further objective of present invention is to provide formulation of Beta-blocker which stabilizes the tear film.

The further objective of present invention is to provide a formulation of Beta-blockers which is effective after longer period of storage.

The further objective of present invention is to minimize/eliminate Beta-blocker entering systemic circulation.

The further objective of present invention is to increase compliance by reduction/elimination of side effects of Beta-blockers.

The further objective of present invention is to provide formulation in a concentration which is known to provide maximum I.O.P. lowering effect in a conventional aqueous formulation.

Accordingly, there is provided a process of manufacturing formulation of topical beta blocker with improved efficacy which comprises of the following steps :

1. The aqueous solution of Beta-blocker is made which contains acceptable excipients, buffers and preservative in distilled water. The pH of this solution is adjusted to 7.0 to 7.5.

2. In a separate vessel Carbopol is dissolved into water and stirred well till gel is formed. Preservatives and buffers are added to it gradually while stirring. The pH of solution is adjusted to pH 6.5 to 7.5.
3. Solution containing Beta-blocker as formulated in step 1 is gradually added to the gel as formed in step 2.
4. Volume is made up by adding distilled water as required.
5. pH is checked and adjusted as necessary to keep it in range of 7.0 ± 0.5 .

Beta-blockers described above can be timolol 0.5%, Betaxolol 0.5%, Levobunolol 0.5%, Cartelol 1.0%, metipranolol 0.3% or any other Beta-blocker which can reduce I.O.P in a therapeutic concentration.

Carbopol can be carbopol 940, 932 970 or others which forms gel in aqueous solution. The concentration of carbopol in final formulation can be from 0.5% to 5%.

The buffer which can be used, can be any, used in topical ophthalmic preparation e.g. dibasic sodium phosphate sodium phosphate mono basic etc.

The preservative can be EDTA, Benzyloconium chloride, Cetrimide or any other which can be used in ophthalmic topical preparation in a dosage recommended.

pH is usually acidic and needs to be adjusted by sodium hydroxide.

The final product is autoclaved and put into a sterile packaging.

Example of formulation**I. Timolol 0.5%**

| | |
|-------------------------------|---|
| Timolol maleate | 0.72 gm equivalent to 0.5 gm of timolol |
| Benzylconium chloride | 0.0107 gm |
| Carbopol 940 | 2.0 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | QS to make 100 ml. |

II. Betaxolol 0.5%

| | |
|-----------------------------|---|
| Betaxolol hydrochloride | 0.56 gm equivalent to 0.5 gm of Betaxolol |
| Benzylconium chloride | 0.01 gm |
| Di basic sodium phosphate | 0.05 gm |
| Sodium phosphate mono basic | 0.025 gm |
| Di sodium EDTA | 0.05 gm |
| Sodium chloride | 0.30 gm |
| Propylene glycol | 2.50 gm |
| Carbopol 940 | 2.00 gm |
| Water for injection | QS to make 100 ml of solution |

The pharmaceutical composition so manufactured is evaluated for stability and efficacy.

The pharmaceutical composition so manufactured is evaluated at different test conditions of temperature and humidity (45° C, 37° C at 80% relative humidity and ambient temperature), for time interval extending upto 12 months.

The samples of formulation were taken for study.

The formulation of timolol 0.5% made as described (new formulation) was evaluated in healthy volunteers as well as in eyes having raised intraocular pressure.

In a single dose paralleled study timolol 0.5% eye drops (conventional formulation) were instilled in one eye and new formulation was instilled in the other eye of 11 patients. Timolol eye drops caused drop in I.O.P. by 23.49% while new formulation caused drop in I.O.P. by 38.7%.

In a single dose cross over study (10 eyes) new formulation as well as conventional formulation (eye drops) were instilled in same eye on different days, but at the same time of day. It was found that reduction in I.O.P. with conventional formulation was 22.36% while that with new formulations was 37.7%.

Thus improved efficacy of new formulation is established in healthy volunteers.

Similarly, in glaucomatous eyes (14), both formulations (conventional and new) were evaluated. Even in glaucomatous eyes the reduction in I.O.P. noticed was much more than that seen with conventional formulation. With conventional formulation it was 33.35% while with new formulation drop in I.O.P. was 44.4%.

The effect on reduction in I.O.P. seen in glaucomatous eyes was further evaluated by long term application in 14 eyes. It was found that effect is maintained even on long term application. The drop in I.O.P. in glaucomatous eyes was 44.4% at 15 days, 43.6% at one month and 43.6% at three months interval.

Thus new formulation was found to have improved efficacy in glaucomatous eyes. This improved efficacy was found to persist even on long terms application.

Like eye drops of timolol, increasing concentration of timolol in new formulation from 0.5% to 1.0%, further drop in I.O.P. was not seen. However, this resulted in increase in duration of its action.

When other antiglaucoma drugs were added to therapy in persons using new formulation it was found to reduce I.O.P. further. This further reduction in I.O.P. was as good as seen with combination of antiglaucoma drugs with timolol eye drops.

Similarly, when formulation with other Beta-blockers like, Betaxolol were made as per process described in this invention it was also found to cause further drop in I.O.P. compared to conventional formulation.

Traditionally made viscous formulation for use as topical ophthalmic preparations are known to cause disturbances in vision. However, none of the person in whom new formulation were used complained of visual disturbances 5 minutes after instillation of new formulation.

1. A process of manufacturing of formulation of topical beta blockers with improved efficacy comprising the following steps :
 - i) a. Making aqueous solution of Beta-blocker with or without physiologically acceptable excipients, buffers and preservatives.
 - b. Making a gel of known gel forming substance with or without physiologically acceptable excipients buffers and preservatives in a separate vessel.
- ii) Adding aqueous solution of Beta-blockers at step i(a) into a prepared gel of step i(b) while stirring slowly.
- iii) Adjusting the pH and volume before finally autoclaving and packaging.
2. A process as claimed in claim 1 wherein Beta-blockers can be selected from topical Beta-blockers used to reduce intraocular pressure, e.g. Timolol, Betaxolol, Carteolol, Metipranolol.
3. A process as claimed in claim 1 & 2 wherein gel forming agent can be carbopol.
4. A process as in claim 1 to 3 wherein concentration of carbopol can be from 0.5% to 5%.
5. A process as claimed in claim 1 to 4 in which physiologically acceptable buffers, excipients and preservatives are used.
6. A process as claimed in claim 1 to 5 wherein pH of formulation is finally adjusted to between 6.0 to 8.0 preferably between 6.5 and 7.5.
7. A process as claimed in claim 1 to 6 wherein formulation is autoclaved before packaging.
8. A process as claimed in claim 1 and substantially herein described in example I & II in the accompanying specification.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 99/00378

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: A 61 K 31/13, 47/00, 31/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: A 61 K 31/13, 47/00, 31/78

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| A | EP 0 227 494 A1 (LABORATOIRES MERCK, SHARP & DOHME-CHIBRET) 01 July 1987 (01.07.87), claims 1,2,10,15. | 1,2,5 |
| A | EP 0 332 147 A2 (WARNER-LAMBERT COMPANY) 13 September 1989 (13.09.89), page 3, lines 21-28. | 1,2,5 |
| A | EP 0 582 321 A1 (GRAMER) 09 February 1994 (09.02.94), column 2, lines 35-49; column 6, lines 16-34; claims 1,4. | 1,2,5 |
| A | Chemical Abstracts, Vol.124, No.26, 24 June 1996 (Columbus, Ohio, USA), page 662, column 1, abstract No.352524c, DICKSTEIN et al.: "Comparison of the effects of aqueous and gellan ophthalmic timolol on peak exercise performance in middle-aged men", & Anm.J.Ophthalmol. 1996, 121(4), 367-371 (Eng). | 1 |
| | ----- | |

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

„A“ document defining the general state of the art which is not considered to be of particular relevance

„E“ earlier application or patent but published on or after the international filing date

„L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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„T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

„X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

„Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

07 March 1999 (07.03.99)

Date of mailing of the international search report

29 June 1999 (29.06.99)

Name and mailing address of the ISA/AT

Austrian Patent Office

Kohlmarkt 8-10; A-1014 Vienna

Faxsimile No. 1/53424/200

Authorized officer

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Telephone No. 1/53424/435

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/00378

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

Claims shall not, except where absolutely necessary, rely, in respect of the technical features of the invention, on references to the description of drawings.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IB 99/00378

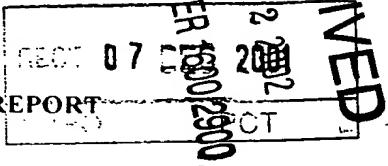
| La Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche | Datum der Veröffentlichung Publication date Date de publication | Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets | Datum der Veröffentlichung Publication date Date de publication |
|--|--|--|--|
| EP A1 227494 | 01-07-1987 | AT E 72990 AU A1 63189/86 AU B2 595240 CA A1 1280367 CN A 86106637 CY A 1779 DE CO 3684121 DK AO 4698/86 DK A 4698/86 DK B1 170500 EP TD 227494 EP B1 227494 ES AF 2002401 FI AO 863990 FI A 863990 FI B 91217 FI C A1 2588189 FR B1 2588189 GR A 862444 HK A 425/94 IE B 59464 IL AO 80156 IL A1 80156 JP A2 62181228 JP B4 6067853 KR B1 9400229 LU A9 88694 LV A4 5725 LV B4 5725 NO A0 863916 NO A 863916 NO B 173212 NO C 173212 NZ A 217662 PT A 83471 PT B 83471 US A 4861760 ZA A 8607464 | 15-03-1992 09-04-1987 29-03-1990 19-02-1991 08-04-1987 20-10-1995 09-04-1992 02-10-1986 04-04-1987 02-10-1995 17-03-1988 04-03-1992 01-08-1988 02-10-1986 04-04-1987 28-02-1994 10-06-1994 10-04-1987 02-12-1988 27-01-1987 13-05-1994 23-02-1994 31-12-1986 17-09-1990 08-08-1987 31-08-1994 12-01-1994 29-04-1996 20-02-1996 20-04-1996 02-10-1986 06-04-1987 09-08-1993 17-11-1993 26-02-1990 01-11-1986 30-11-1988 29-08-1989 29-07-1987 |
| EP A2 332147 | 13-09-1989 | AT E 90571 AU A1 30258/89 AU B2 611771 DE CO 68907081 DE T2 68907081 DK AO 1096/89 DK A 1096/89 EP A3 332147 EP B1 332147 EP B1 499662 ES T2 2056981 GR T2 3014988 IE B 62871 JP A2 1272519 NZ A 228094 PH A 26548 ZA A 8901031 US A 5019395 AU A1 70061/91 AU B2 634015 AT E 114481 DE CO 69105480 DE T2 69105480 DK T2 499662 EP A1 499662 JP A2 4338325 ZA A 9100624 | 15-07-1993 14-09-1989 20-06-1991 22-07-1993 21-10-1993 07-03-1989 09-09-1989 19-09-1990 16-06-1993 30-11-1994 16-10-1994 31-05-1995 08-03-1995 31-10-1989 25-09-1991 19-08-1992 21-10-1990 28-05-1991 20-08-1992 11-02-1993 15-12-1994 12-01-1995 06-04-1995 15-05-1995 26-08-1992 25-11-1992 28-10-1992 |
| EP A1 582321 | 09-02-1994 | DE A1 4201079 DE CO 4201079 DE C1 4201079 EP A1 556565 EP A3 556565 US A 5459140 | 22-07-1993 14-12-1995 11-09-1997 25-08-1993 01-12-1993 17-10-1995 |

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



| | | |
|---|--|--------------------------------|
| Applicant's or agent's file reference | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. | International filing date (day/month/year) | Priority Date (day/month/year) |
| PCT/IB 99/00378 | 4 March 1999 (04.03.1999) | 11 December 1998 (11.12.1998) |
| International Patent Classification (IPC) or national classification and IPC | | |
| IPC ⁷ : A61K 31/13, 47/00, 31/78 | | |
| Applicant KHAMAR, Bakulesh Mafatlal | | |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examination Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>4</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 507 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of _____ sheets.</p> | | |
| <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I. <input checked="" type="checkbox"/> Basis of the opinion II. <input type="checkbox"/> Priority III. <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV. <input type="checkbox"/> Lack of unity of invention V. <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI. <input type="checkbox"/> Certain documents cited VII. <input type="checkbox"/> Certain defects in the international application VIII. <input type="checkbox"/> Certain observations on the international application | | |

| | |
|---|---|
| Date of submission of the demand | Date of completion of this report |
| 6 July 2000 (06.07.2000) | 1 February 2001 (01.02.2001) |
| Name and mailing address of the IPEA/AT Austrian Patent Office Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/200 | Authorized officer MOSSER Telephone No. 1/53424/437 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/IB 99/00378

1. Basis of the report

1. With regard to the **elements** of the international application:*

the international application as originally filed

the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement) under Article 19

pages _____, filed with the demand

pages _____, filed with the letter of _____

the drawings:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

the language of publication of the international application (under Rule 48.3(b)).

the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

contained in the international application in printed form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

the description, pages _____

the claims, Nos. _____

the drawings, sheets/fig. _____

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(e)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as „originally filed“ and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,
 claims Nos. 8

because:

~~the said international application, or the said claims Nos.~~ ~~relate to the following subject matter which does not require an international preliminary examination (specify):~~

The search report and the examination report have not been established in respect of claim 8, because this claim contains a reference to examples, only and does not express any further technical features of the invention.

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

the written form has not been furnished or does not comply with the standard.
 the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORTInternational application No.
PCT/IB 99/00378**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

| | | |
|--|------------|-----|
| 1. Statement | | |
| Novelty (N) | Claims 1-7 | YES |
| | Claims | NO |
| Inventive step (IS) | Claims 1-7 | YES |
| | Claims | NO |
| Industrial applicability (IA) | Claims 1-7 | YES |
| | Claims | NO |
| Citations and explanations (Rule 70.7) | | |

The documents which are cited in the search report do not interfere with novelty and inventive step of the subject matter of the present claims 1-7. The industrial applicability is self-evident for the subject-matter of these claims.

The search report and the examination report have not been established in respect of claim 8, because this claim contains a reference to examples only and does not express any further technical features of the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 99/00378

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: A 61 K 31/13, 47/00, 31/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: A 61 K 31/13, 47/00, 31/78

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| A | EP 0 227 494 A1 (LABORATOIRES MERCK, SHARP & DOHME-CHIBRET) 01 July 1987 (01.07.87), claims 1,2,10,15. | 1,2,5 |
| A | EP 0 332 147 A2 (WARNER-LAMBERT COMPANY) 13 September 1989 (13.09.89), page 3, lines 21-28. | 1,2,5 |
| A | EP 0 582 321 A1 (GRAMER) 09 February 1994 (09.02.94), column 2, lines 35-49; column 6, lines 16-34; claims 1,4. | 1,2,5 |
| A | Chemical Abstracts, Vol.124, No.26, 24 June 1996 (Columbus, Ohio, USA), page 662, column 1, abstract No.352524c, DICKSTEIN et al.: "Comparison of the effects of aqueous and gellan ophthalmic timolol on peak exercise performance in middle-aged men", & Ann.J.Ophthalmol. 1996, 121(4), 367-371 (Eng). | 1 |
| | ---- | |

Further documents are listed in the continuation of Box C.

See patent family annex.

| | |
|--|---|
| * Special categories of cited documents: ..A" document defining the general state of the art which is not considered to be of particular relevance | ..T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| ..E" earlier application or patent but published on or after the international filing date | ..X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| ..L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | ..Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| ..O" document referring to an oral disclosure, use, exhibition or other means | |
| ..P" document published prior to the international filing date but later than the priority date claimed | ..&" document member of the same patent family |

| | |
|--|---|
| Date of the actual completion of the international search 07 March 1999 (07.03.99) | Date of mailing of the international search report 29 June 1999 (29.06.99) |
| Name and mailing address of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200 | Authorized officer Mosser Telephone No. 1/53424/435 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/00378

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:
Claims shall not, except where absolutely necessary, rely, in respect of the technical features of the invention, on references to the description of drawings.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IB 99/00378

| Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche | Datum der Veröffentlichung Publication date Date de publication | Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets | Datum der Veröffentlichung Publication date Date de publication |
|---|--|--|--|
| EP A1 227494 | 01-07-1987 | AT E 72990 AU A1 63189/86 AU B2 595240 CA A1 1280367 CN A 86106637 CY A 1779 DE CO 3684121 DK A0 4698/86 DK A 4698/86 DK B1 170500 EP TD 227494 EP B1 227494 ES AF 2002401 FI A0 863990 FI A 863990 FI B 91217 FI C A1 91217 FR A1 2588189 FR B1 2588189 GR A 862444 HK A 425/94 IE B 59464 IL A0 80156 IL A1 80156 JP A2 62181228 JP B4 606785 KR B1 9400229 LU A9 88694 LV A4 5725 LV B4 5725 NO A0 863916 NO A 853916 NO B C 173216 NO C 173216 NZ A 217862 PT A 83471 PT B 83471 US A 4861760 ZA A 8607464 | 15-03-1992 09-04-1987 29-03-1990 19-02-1991 08-04-1987 20-10-1995 09-04-1992 02-10-1986 04-04-1987 02-10-1995 17-03-1988 04-03-1993 01-08-1988 02-10-1986 04-04-1987 28-02-1994 10-06-1994 10-04-1987 02-12-1988 27-01-1987 13-05-1994 23-02-1994 31-12-1986 17-06-1990 08-08-1987 31-08-1994 12-01-1994 26-04-1996 20-02-1996 20-08-1996 02-10-1986 06-04-1987 09-08-1993 17-11-1993 26-02-1990 01-11-1986 30-11-1988 29-08-1989 29-07-1987 |
| EP A2 332147 | 13-09-1989 | AT E 90571 AU A1 30258/89 AU B2 611771 DE CO 68907081 DE T2 68907081 DK A0 1096/89 DK A3 1096/89 EP A3 332147 EP B1 332147 EP B1 499662 EP T2 2056981 EP T2 3014988 IE B2 62871 JP A2 1272519 NZ A 228094 PH A 28548 ZA A 8901031 US A 5019395 AU A1 70061/91 AU B2 634015 AT ECO 114481 DE CO 69105480 DE T4 69105480 DK T4 499662 EP A1 499662 JP A2 4338357 ZA A 9100624 | 15-07-1993 14-09-1989 20-06-1991 22-07-1993 21-10-1993 07-05-1989 09-06-1989 19-09-1990 16-06-1993 20-11-1994 16-10-1994 31-05-1995 08-03-1995 21-10-1999 25-09-1991 19-08-1992 31-10-1990 28-05-1991 20-05-1992 11-05-1993 15-12-1994 12-01-1995 06-04-1995 15-05-1995 26-08-1992 25-11-1993 28-10-1992 |
| EP A1 582321 | 09-02-1994 | DE A1 4201079 DE CO 4201079 DE CO 4201079 DE A3 556566 DE A3 556566 US A 5459140 | 22-07-1993 14-12-1995 11-05-1997 25-08-1993 01-12-1993 17-10-1995 |

PATENT COOPERATION TREATY

PCT

**INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION**
(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

KHAMAR, Bakulesh, Mafatlal
201 "Ashadha", Vasundhara Colony
Gulbai Tekra, Ellisbridge
Ahmedabad 380 006
INDE

| |
|----------------------------------|
| Date of mailing (day/month/year) |
| 20 September 2000 (20.09.00) |

| | | | |
|--|--|--------------------------------|--|
| Applicant's or agent's file reference | | IMPORTANT INFORMATION | |
| International application No. | International filing date (day/month/year) | Priority date (day/month/year) | |
| PCT/IB99/00378 | 04 March 1999 (04.03.99) | 11 December 1998 (11.12.98) | |
| Applicant KHAMAR, Bakulesh, Mafatlal | | | |

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW
 EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
 National :AU,BG,CA,CN,CZ,DE,IL,JP,NZ,PI,RO,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
 National :AT,BR,CH,CU,DK,EE,ES,FI,GB,GE,GH,ID,KE,KZ,LT,LV,MD,MW,MX,SD,TT,
 UA,UG,UZ,VN

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until **31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
 Olivia TEFY

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and
Administrative Instructions, Sections 402 and 409)

From the INTERNATIONAL BUREAU

To:

KHAMAR, Bakulesh, Mafatlal
201 "Ashadha", Vasundhara Colony
Gulbai Tekra, Ellisbridge
Ahmedabad 380 006
INDE

Date of mailing (day/month/year)
28 May 1999 (28.05.99)

Applicant's or agent's file reference

IMPORTANT NOTIFICATION

International application No.
PCT/IB99/00378

International filing date (day/month/year)
04 March 1999 (04.03.99)

Applicant

KHAMAR, Bakulesh, Mafatlal

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application.

1. **Correction of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been corrected to read as follows:
 - even though the indication of the number of the earlier application is missing.
 - even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
2. **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:
 - even though the indication of the number of the earlier application is missing.
 - even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
3. As a result of the correction and/or addition of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:
4. **Priority claim considered not to have been made.**
 - The applicant failed to respond to the Invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.
 - The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).
 - The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.

The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(B).
5. In case where multiple priorities have been claimed, the above item(s) relate to the following priority claim(s):

IN 02 December 1997 (02.12.97) 699/Bom/9
6. A copy of this notification has been sent to the receiving Office and
 - to the International Searching Authority (where the international search report has not yet been issued).
 - the designated Offices (which have already been notified of the receipt of the record copy).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Maria Victoria CORTIELLO

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)Date of mailing (day/month/year)
20 September 2000 (20.09.00)To:
Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

International application No.
PCT/IB99/00378

Applicant's or agent's file reference

International filing date (day/month/year)
04 March 1999 (04.03.99)Priority date (day/month/year)
11 December 1998 (11.12.98)Applicant
KHAMAR, Bakulesh, Mafatlal1. The designated Office is hereby notified of its election made: in the demand filed with the International Preliminary Examining Authority on:

06 July 2000 (06.07.00)

 in a notice effecting later election filed with the International Bureau on:2. The election was was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35Authorized officer
Olivia TEFY
Telephone No.: (41-22) 338.83.38